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CLINICAL REVIEW

Actigraphy for measurements of sleep in relation to oncological treatment of patients with cancer: A systematic review

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SUMMARY

Sleep disturbances are a prevalent and disabling problem for patients with cancer. Sleep disturbances are present throughout the cancer trajectory, especially during oncological treatment. Previously sleep disturbances have primarily been quantified with subjective rating scales. Actigraphy is an easy to use, non-invasive method for objective measurement of sleep.

We systematically reviewed the literature for studies using actigraphy to measure sleeping habits of patients with cancer, undergoing oncological treatment. Our study furthermore reviewed studies with interventions designed to reduce sleep disturbances in the patient population. 19 studies were included in the final review of which 13 had a descriptive study design and six included some kind of intervention. The studies were primarily performed in patients with breast cancer undergoing chemotherapy. We found that sleep disturbances are prevalent, and persistent in patients with cancer. The sleep disturbances seem to be aggravated by chemotherapy treatment and accumulate as the treatment continues. Sleep disturbances need further attention among clinicians working with patients with cancer.

Introduction

Sleep disturbances are frequent for many patients with cancer, [1–3] and have a substantial effect on their daily lives. Sleep and sleep-wake disturbances have been diagnosed in connection to cancer surgery [4], before the initiation of chemotherapy regimens [5,6], during cancer treatment [7], and also among cancer survivors [8–10]. Often patients do not report their sleep complaints to the clinician and up to half of the patients do not believe that anything can be done to help them with this problem [11,12].

Sleep disturbances rarely represent an isolated problem for patients with cancer, and are often part of larger symptom clusters [13]. Patients with cancer suffer from fatigue, depression, and anxiety, which all, along with sleep disturbances, are contributing factors to reduced quality of life [14,15]. The prognosis for patients with cancer has improved for certain types of cancer over the last few decades [16,17], which results in a growing number of people living as cancer survivors. This fact means an increased need for clinicians to focus on these symptom clusters in patients with cancer and cancer survivors. Sleep disturbances are especially prominent during oncological treatment [18–20], and therefore clinicians need to pay extra attention to these underdiagnosed side-effects of the oncological treatment [21]. As sleep disturbances are aggravated during oncological treatment [18–20] this period will be the specific focus of the current review. Furthermore, a recent review [1] showed that the majority of studies measuring sleep in this population only measure sleep subjectively. We therefore chose to focus on objective sleep measurements by the use of actigraphy.

Actigraphy is a methodology which is used to quantify sleep and circadian rhythms, and its use among researchers and clinicians has increased over the last two decades [22]. Some of the reasons for the increased popularity of actigraphy are the non-invasive methodology, low cost, and simultaneous ability to objectively measure sleep and circadian rhythms. Actigraphy has been shown to have high correlation with polysomnography (PSG) which is the gold standard in sleep assessment [22]. The mobile and non-invasive properties of an actigraph unit is ideal for measuring sleep disturbances in patients with cancer in an ambulatory setting [23].

The aim of this paper is to systematically review research studies conducted in patients with cancer who are undergoing oncological treatment while having sleep quantified by actigraphy;

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Abbreviations

AASM	American Academy of Sleep Medicine
ADT	androgen therapy
CBT	cognitive behavioral therapy
DTS	daytime sleep
EASE	energy and sleep enhancement
ISI	insomnia severity index
ISPP	individualized sleep promotion plan
NOA	number of awakenings
PSG	polysomnography
PRISMA	Preffered reporting items for systematic reviews and meta-analyses
PSQI	Pittsburgh sleep quality index
SE	sleep efficiency
SL	sleep latency
TST	total sleep time
TWT	total wake time
TIB	time in bed
WASO	wake after sleep onset
ZCM	zero crossing mode

Glossary

Chemotherapy cycle (CC)
: A cycle of chemotherapy administration last either two or three weeks depending on the individual regime. Each patient receives several cycles of chemotherapy depending on the type of cancer and the clinical response to treatment.

Daytime sleep (DTS)
: defined as the amount of time during the daytime scored as sleep

Number of awakenings (NOA)
: is the number of awakenings during the sleep period with a predefined duration of minimum 5 min

Sleep efficiency (SE)
: is the percentage of actual sleep while being in bed at night

Sleep latency (SL)
: is the time from "lights-off" until the actual time of sleep onset

Time in bed (TIB)
: the amount of time spent in bed, hence longer than total sleep time

Total sleep time (TST)
: describes the duration of the sleep period based on the actual sleep start and end, and not the time spent in bed

Total wake time (TWT)
: defined as the amount of time during the daytime scored as wake

Wake after sleep onset (WASO)
: is the wake time in minutes after sleep onset, which for healthy adults typically is 25 min each night

hereby describing the effect of oncological intervention on patients sleep. A secondary aim is to describe studies with interventions designed to alleviate or reduce the present sleep disturbances.

Method

The search for litterature for this systematic review was performed in four databases: Medline, Embase, Cinahl and PsycInfo. All of the searches were conducted by the 2nd of January 2014. Keywords relating to the disease, and the method, and period of oncological treatment were searched. The following terms were used in the search for eligible studies: "cancer patient OR oncological patient OR cancer OR neoplasm" AND "actigraphy OR actigraph OR actigraph* OR actigraphy recording OR wrist actigraphy OR actometer OR actimeter OR actical OR actiwatch OR sleep watch OR motion logger" AND "chemotherapy OR oncological treatment OR cancer chemotherapy OR new adjuvant chemotherapy OR adjuvant chemotherapy OR radiation OR radiation therapy OR cancer radiation OR oncological agent".

The following inclusion criteria were used to identify studies: the study must contain actigraphy measurements in its design, the study population must receive some kind of oncological treatment (e.g., chemotherapy, radiation therapy or hormone treatment), and the study should include an actigraphy determined sleep outcome. The following exclusion criteria were used to identify studies: the study should be published in English and in a peer reviewed journal, the study must be an original study containing original data (no protocol articles or duplicate publications), and the study population must 18 y or older.

Title and abstracts were assessed according to the inclusion and exclusion criteria by two reviewers (MTM and CH). When assessed on title and abstract level, circadian outcomes measured by actigraphy were included due to the possibility of co-reporting of sleep outcomes. If the two reviewers disagreed, a decision was reached within the whole author group. The studies selected for full text evaluations were then evaluated according to inclusion and exclusion criteria by both of the reviewers (MTM and CH). After full text evaluation of the studies, the study design, patient characteristics, cancer treatment, timing of measurements and individual outcomes were documented and condensed into tables.

Furthermore, to evaluate the methodological level of actigraphy measurements, details about these were extracted from the studies and afterwards evaluated according to the guidelines put forth by Berger et al. [24]. These guidelines focus on methodological challenges that arise when using actigraphy e.g., instrumentation, sampling, data processing, and analysis. The risks of bias and study quality were evaluated according to Downs and Black [25]; an evaluation tool used to assess both non-randomized and randomized trials. The studies are evaluated with regard to overall study quality, external validity, internal validity (bias), confounding, and power using 27 distinct questions. Each study was given a summarized score from 0 to 33 with higher scores indicating higher study quality. This study was conducted according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines for systematic reviews [26].

Results

A total of 191 studies were identified through Medline, Embase, Cinahl and PsycInfo (Fig. 1). After the removal of duplicates, 100 studies were evaluated based on abstract and title. Out of these, 54 studies were excluded. Out of the 54 excluded studies 16 involved children, four studies had no relevant outcomes, three studies had no cancer diagnosis, eight studies no oncological treatment, three were reviews, 15 were conference abstracts, and five were dissertations. Of the 46 articles selected for full text assessment, another 27 were excluded. Two papers were excluded due to duplicate data, five papers contained no oncological treatment, ten papers only

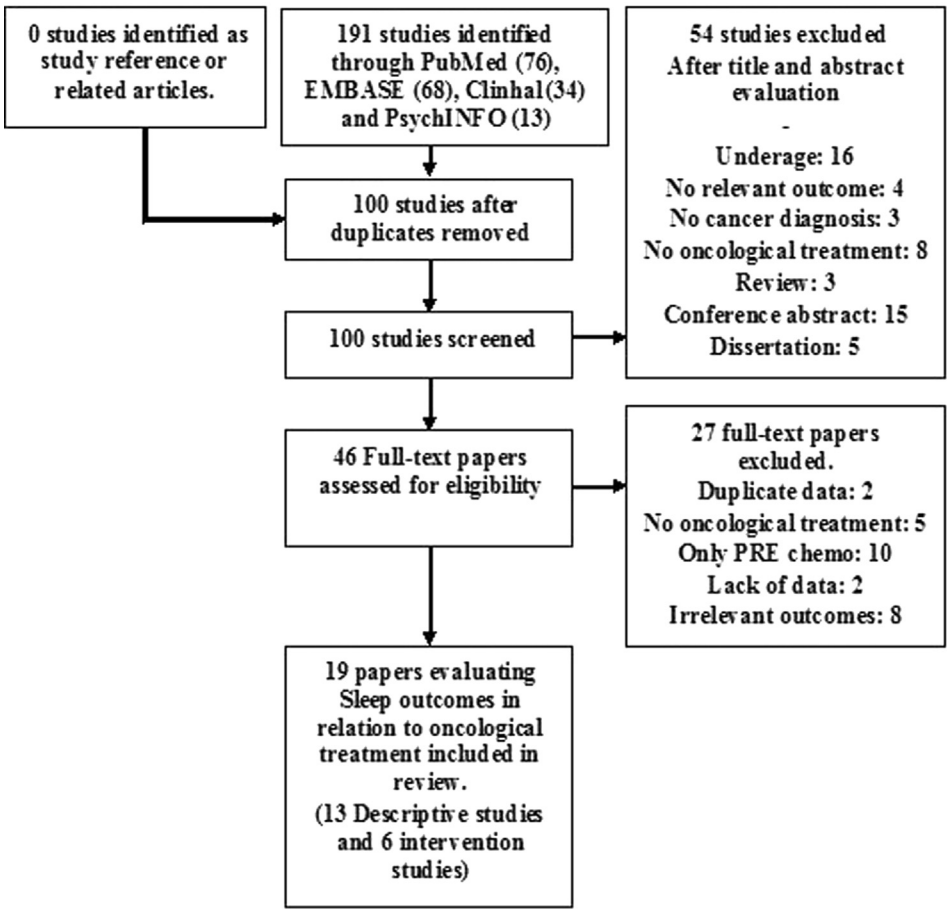

Fig. 1. Flowchart for systematic review of actigraphy and cancer.

had pre-chemotherapy actigraphy measurements, two papers lacked data, and eight papers reported irrelevant outcomes.

Left were a total of 19 relevant articles describing sleep of which 13 studies were descriptive studies and six studies were intervention studies. The 13 descriptive studies clarify the effect of oncological treatment on patients, sleep, and are hereafter referred to as oncological treatment studies. The six studies including a sleep improving intervention are referred to as sleep intervention studies. Due to considerable heterogeneity in the actigraphy data reported in the randomized clinical trials it was not possible to perform a meta-analysis.

Oncological treatment studies

Of the 19 included sleep studies 13 were oncological treatment studies (Table 1). Eight studies were performed in patients with breast cancer [27–34], one gynecological cancer [35], one colorectal cancer [36], one prostate cancer [37], one lung cancer [38], and one involving mixed cancer populations [39]. The 13 studies were conducted between 1999 and 2012. The smallest study included 13 patients and the largest included 183 patients. Of the 13 studies nine used a longitudinal repeated-measure design and four used a cross sectional study design (Table 1). It should be noted that the article published by Liu et al. [27] is a combination of unpublished data from two studies [30,40]. Likewise, the data presented in [34] represents secondary data from two sleep intervention studies [41,42].

Breast cancer population

Of the eight studies including patients with breast cancer [27–34] the population size was between 16 and 183. In seven of these studies [27,29–34] patients received chemotherapy, and in the last study [28] patients underwent adjuvant radiation therapy. Patient characteristics were cancer stage I to III, no known sleep disorders or psychological disorders. The chemotherapy regimens were predominantly antracyclin based, and patients who underwent radiation therapy received an average of 58 Gy (Table 1). With regards to the timing of actigraphy measurements, only one study [28] measured pre-, during-, and post-radiation therapy. Five studies with chemotherapy measured pre- and during chemotherapy [27,29–32], and two measured only during chemotherapy [33,34]. Both a varying length of individual measurements and the number of measurement periods were present in the breast cancer group (Table 1). Even though six out of eight studies of patients with breast cancer included pre-treatment measurements, exploring the longitudinal development of sleep was difficult due to measurements being made in different cycles and weeks of each cycle in the chemotherapy treatment.

Three studies [30,32,34] described total sleep time (TST) on the first week of cycle 1, and observed that TST initially was reduced but then increased compared to pre-treatment values [30]. During week 2 and 3 of cycle 1, TST was unchanged compared to pre-treatment measurements [29]. Cycle 4 showed the same pattern with increased TST in week 1 [30] and then similar measurements to pre-treatment values in weeks 2 and 3 [29]. Even though there

Table 1
Oncological treatment studies.

Author	*N*	Control group	Cancer type	Characteristics	Cancer treatment	Timing of measurement			Outcome							Other (absolute values)
						Pre	During	Post	TST	TWT	NAPTIME	WAKE	WASO	NOA	SE	
Liu L et al., 2013 [27]	166	None	Breast	Stage 1–3, non-metastatic, no psychological diagnosis	Chemotherapy (minimum 4 CYL. antracyclin)	1	1 (C4W3)	0	↑	↔	↔	NS	NS	NS	NS	Baseline: TST < 7 h, TWT > 2 h and NAPTIME > 1 h
Dhruva A et al., 2012 [28]	73	None	Breast	Non-metastatic, only one cancer, no sleep disorder	Adjuvant radiation therapy (RT)	1	1	1	NS	NS	NS	NS	↔	NS	NS	Baseline: TST 7 h, SL 14.7 min, SE 85.5%, NOA 15.1
Liu L et al., 2012 [29]	53	None	Breast	Stage 1–3, no previous chemo, non-metastasis	Chemotherapy (3 wk, antracyclin based)	1	1 (C1W2+3 and C4W2+W3)	0	↔	↔	↑ C4W2	NS	NS	NS	NS	Baseline: TST < 7 h, TWT > 2 h and NAPTIME > 1 h
Liu L et al., 2012 [30]	97	None	Breast	Stage 1–3, no previous chemo, non-metastasis	Chemotherapy (3 wk, antracyclin)	1	1 (C1W1+ C4W1)	0	↑ C1W1 + C4W1	↔	↑ C1W1 + C4W1	↓ C1W1 + C4	NS	NS	NS	NS
Jim H.S. et al., 2011 [35]	78	None	Gynecological	Stage 1–4, primarily first-line chemotherapy, no psychiatric dis.	Chemotherapy (Platinum-based combi)	1	1 (C1W1+3, C2W1+3, C3W1)	0	NS	NS	↑ (After infusion)	NS	↑ (After infusion)	NS	↔	TIB ↑ after infusion
Hanisch LJ. et al., 2011 [37]	60	None	Prostate	Metastasis, biomarker progress and localized disease	ADT (Leuprolide, bicalutamide and ketoconazole)	0	1	0	5.9 h	NS	58.8 min	NS	49.4 min	NS	75%	Absolute values: SL: 43 min NON: 3.7
Rissling MB. et al., 2011 [31]	69 (12/21/36)	None	Breast (pre, peri + post menupau.)	Stage 1–3, non-metastasis, no psychological diagnosis	Chemotherapy (3 wk, antracyclin based)	1	1 (C4W3)	0	↓	NS	NS	NS	↑	↑	↓	Pre menopausal vs post menopausal. Pre menopause more disturbed sleep
Berger AM. et al., 2010 [36]	13 (24)	Yes (Historic data)	Colorectal	Stage 2–4, no sleep disorder, no co-morbidities no previous sleep problems. No shift work	Chemotherapy (5-FU, FOLFOX or 5-fu + leucovorin)	0	1 (cycle 1, 2, 3 all W1)	0	↔	NS	NS	NS	↑	↑	↓	Patient vs. healthy controls: No sign. trend during chemo
Beck sl. et al. 2010 [34]	183 (101/82)	None	Breast cancer	Stage 1–3, no prior chemo, no sleep disorder, psychological disease or shift-work	Chemo; antrocyclin and/or cyclophospamid	0	1 (C1D1–3)	0	↓ C1N1 ↔ C1N2 + C1N3	NS	NS	NS	↔	C1N1 ↑ C1N2+3 ↔	↔	NS
Du-Quiton J. et al., 2010 [38]	68	35 Healthy adults	Advanced NSCLC	Stage 2–4, unresectable, PS 0–2, no brain metastasis	Chemotherapy (Cisplatin and etoposide/4W cycle)	1(out pt)	1 (in pt)	0	↓	NS	↓	↓	↑	NS	↓	Cancer patients vs. Controls: No sign. change over time

Payne JK et al., 2006 [32]	22	11 healthy adults	Breast cancer	Stage 2, first chemo admin	Adjuvant chemotherapy (Doxorubin and cyclophosphamid)	1	1 (C1N1+ C4N1+2)	0	↔ C1N1 ↓ C1N2 ↔ C4N1+2	NS	NS		NS	NS	NS	NS	Cancer patients vs. controls: Inverse relationship between melatonin and sleep levels
Kuo HH. et al., 2006 [33]	16	None	Breast cancer	Stage 1–2, no psycological or neurological disorders	Adjuvant chemotherapy (CEF or CMF)	0	1 (C3N8+9 and C4N−2,−1)	0	↔	NS	NS		NS	↔	NS	↔	C3N8+9 (chemo) vs. C4N-2 + −1 82% No chemo: 71% SL: 30 min+TIB: 575 min
									395 min					48 min			
Miaskowski C et al., 1999 [39]	22	None	Mixed cancers	Bone metastasis, opiod use for pain	Radiation therapy	0	1	0	400 min	NS	70% patients	NS		NS	17		

The table shows the descriptive studies describing sleep included in the review.
ADT: Androgen deprivation therapy, CYL: cycle, CxNy: cycle number (x) night number (y), CxWy: cycle number (x) week number (y) of chemotherapy, FOLFOX: folinic acid, fluorouracil and oxiplatin. NAPTIME: total nap time (during the day), NOA: number of awakenings (minimum 5 min duration), NSCLC: non small cell lung carcinoma, NS: not stated, RT: radiation therapy, SE: sleep efficiency (% of time spent in bed), SL: sleep latency (min), SM: sleep minutes (during the day), TIB: time in bed (minutes), TST: total sleep time, TWT: total wake time (during the night), WAKE: wake time (during the day), WASO: wake after sleep onset (min or % of TST), WASO-P: wake after sleep onset (% of TST), WASO-M: wake after sleep onset (minutes), WM: wake minutes (during the day).
↔: no change, ↓: decreased values, ↑: increased values.

were discrepancies in cycle 4 week 3 with one study [31] showing reduced TST, one study [29] reported unchanged TST, and one study [27] reported an increase in TST. The total wake time (TWT) during the night was shown to be stable and unchanged during all of cycle 1 and 4 compared to pre-treatment values [29,30].

After chemo administration an increase in day time sleep (DTS) was observed in both cycle 1 and 4 [29,30]. In cycle 4 the increased daytime sleep was also present in week 2, representing an increased need for sleep as the chemotherapy treatment continues [29,30]. Beck et al. [34] showed that the number of awakenings (NOA) increased on night 1 after chemotherapy and then normalized the following nights in cycle 1. In the same study [34] sleep efficiency (SE) and wake after sleep onset (WASO) were unchanged. The study measuring patients with breast cancer during radiation therapy [28] reported unchanged WASO during the entire radiation treatment as the only sleep outcome.

Other cancer populations

For gynecological patients receiving first-line platinum-based chemotherapy diagnosed with stage I-IV gynecological cancers sleep was reported pre-treatment and during cycle 1, 2 and 3 around infusion times [35]. The study showed that time in bed (TIB) was reduced prior to infusions and then increased after chemotherapy administration. SE was unchanged during the three cycles of chemotherapy whereas WASO and DTS both increased after each chemotherapy infusion.

For the colorectal patient study, [36] no pre-treatment measurements were recorded, and only measurements of the first week of cycle 1, 2 and 3 were reported. No significant change over the three cycles was recorded and compared to healthy controls NOA and WASO were increased, whereas SE was reduced and TST unchanged.

In the study evaluating patients with advanced lung cancer [38] the study population was divided into out-patients and in-patients. The out-patient population was measured pre-chemotherapy, and the in-patient population was measured during first chemotherapy treatment. Compared to healthy controls, the patients with cancer had reduced TST, SE and TIB, and increased WASO and SE.

In the patient population with prostate cancer undergoing androgen therapy (ADT) [37], and patient population of mixed cancers undergoing radiation therapy [39], only measurements during treatment were performed. The studies were cross sectional and only provided absolute sleep values; however, no control group is present, so the application of the study is limited (Table 1).

Sleep intervention studies

Of the 19 included studies, six had an intervention setup (Table 2). Five of the studies [42–46] were performed in patients with breast cancer and one study [41] in a mixed population with cancer (55% breast cancer). The studies were performed between 2002 and 2010, and had a study population between 20 and 219 patients. One study was a quasi experimental feasibility study [43], one was an open label intervention study [46], and four studies [41,42,44,45] were randomized clinical trials without any form of blinding.

In the most recent study [41] an energy and sleep enhancement (EASE) non-pharmacological self-help strategy was applied to test its sleep improving effect during chemotherapy. The study was performed on a mixed cancer population, with 153 patients receiving EASE and 139 receiving control treatment. No effect of EASE was shown on any objective sleep parameter (TST, SE, NOA or WASO). Absolute sleep outcomes did not change throughout chemotherapy, and were within normal values except for NOA. The

Table 2
Sleep intervention studies.

Author	*N*	Control grp.	Intervention	Cancer type	Characteristics	Cancer treatment	Timing of measurement				Outcome						SE	Other (Absolute values)
							Total	Pre	During	Post	TST	TWT	NAPTIME	WAKE	WASO	NOA		
Barsevick A et al., 2010 [41]	292	139	EASE (Psycho-therapy)	Mixed cancer	Stage 1–3a, no sleep disorder, no heart/lung or neuromuscular disease	CTX	2 × 3 d	0	C1D1–4	D43–46/ 57–60	↔	NS	NS	NS	↔	↔	↔	No intergroup diff.
											(465 → 466 min)				(69 → 64 min)	(10 → 10)	(86 → 87%)	
Berger A. et al., 2009 [42]	173	85	Behavioral therapy sleep intervention (ISPP)	Breast	Stage 1–3a, no sleep disorder, no heart/lung or neuromuscular disease	CTX (Antracyclin based)	1 × 2 d + 4 × 7 d	1 (2 d pre)	0	30, 60, 90 d and 1 y post	↔	NS	NS	NS	↔	↑	↔	Intergroup diff.
																(30 + 60 d post)		Sign. differences between actigraphy and sleep diary
Berger A. et al., 2009 [45]	219	105	Behavioral therapy sleep intervention (ISPP)	Breast	Stage 1–3a, no sleep disorder, no heart/lung or neuromuscular disease	CTX (Antracyclin based)	1 × 2 d + 2 × 7 d	1 (2 d pre)	C4D1–7	30 d post	↔	NS	NS	NS	↔	↔	↔	No intergroup diff.
																		Post- vs. pre-+peri-menopausal
											↓				↑	↑	↓	Pre + peri - hot flashes → sleep disturbances
Berger A. et al., 2009 [44]	219	105	Behavioral therapy sleep intervention (ISPP)	Breast	Stage 1–3a, no sleep disorder, no heart/lung or neuromuscular disease	CTX (Antracyclin based)	1 × 2 d + 5 × 7 d	1 (2 d pre)	C1,2,3,4 D1–7	30 d post	↔	NS	NS	NS	↔	↑	↔	Intergroup difference
											(395–465 min)				(7 −15%)	(9–11)	(85–93%)	
Payne JK. Et al. 2008 [46]	20	10	20 min exercise	Breast	Fatigued, age ≥ 55	Hormonal therapy (Tamoxifen, anostrosole + letrozole)	2 × 3 days	0	1st wk and 12th wk	0	↓	↓	NS	NS	NS	NS	↔	(from the intervention group.)
Berger A. et al., 2002 [43]	25	0	ISPP (4-component sleep intervention)	Breast	Stage 1–2, no sleep disorder, no heart/lung or neuromuscular disease	Doxorubicin based	2 days × 1 + 7 days × 1	Day -2,-1	C1D1-4 + C1D5-7	0	↔	NS	↔	NS	↔	↔	↔	No sign. change during chemo therapy.

The table shows the intervention studies describing sleep included in the review.
CTX: chemotherapy, CxDy: cycle number (x) Day number (y), d: days, EASE: energy and sleep enhancement (intervention regime), ISSP: individualized sleep promotion plan, NAPTIME: total nap time (during the day), NOA: number of awakenings (minimum 5 min duration), NS: not stated, SE: sleep efficiency (% of time spend in bed), SL: sleep latency (min), TST: total sleep time, WAKE: wake time (during the day), WASO: wake after sleep onset (min or % of TST), WASO-M: wake after sleep onset (minutes), WASO-P: wake after sleep onset (% of TST).
↔: no change, ↓: decreased values, ↑: increased values.

article explains the lack of effect of the intervention by heterogeneity in the study population, variability in dose of intervention, wrong timing of measurement, and a floor effect for objective sleep measures (i.e., no sleep disturbances were present in the population, so the intervention had no effect).

Three articles [42,44,45] reported results from the same study population, but at different time points of the chemotherapy treatment. Two studies [44,45] reported results during the chemotherapy and one [42] reported post treatment conditions. The intervention in this study was an individualized sleep promotion plan (ISPP) tested in the feasibility study described earlier [43]. The only significant time by group difference was shown for NOA in [44] and only tendencies for improved sleep in the intervention group for TST and SE. The absolute sleep values for TST and SE during the first four cycles and 30 d after were within normal values [44], representing close to normal sleep; however, WASO and NOA were higher than healthy controls. The results reported in the post treatment phase (30, 60, 90 and 365 d post) confirmed that there was no group (ISPP vs. control) difference in TST, SE or WASO [42]. The ISPP group however, had an increased NOA 30 and 60 d after treatment [42], but this difference was not present at 90 or 365 d. In a secondary analysis [45] where study participants were pooled according to menopausal status (pre-, peri-, and post-menopausal) it was shown that TST and SE were increased and NOA and WASO reduced in the post menopausal subgroup throughout chemotherapy treatment (four cycles and 30 d post). Throughout the three studies [42,44,45] a consequent discrepancy between objectively (actigraphy) and subjective measures of sleep (sleep diary) was present. Generally the intervention group (ISPP) had better subjectively measured sleep (diaries and Pittsburgh sleep quality index – PSQI) compared to controls.

The feasibility study [43] had a small study population of only 25 patients and no control group. The intervention was an individualized sleep promotion plan (ISPP), consisting of four non-pharmacological strategies to improve sleep and was administered by trained nurses at predefined points throughout the chemotherapy treatment. The study showed no significant change in sleep (TST, NOA, WASO, SL (sleep latency) and SE) over four cycles of doxorubicin based chemotherapy measured 2 d pre and 7 d post treatment. 30, 60, 90 and 365 d outcomes were reported in a separate publication [47], which is not included in this review because it did not include actual chemotherapy treatment.

The open label study [46] also had a small study population consisting of 10 intervention and 10 control observations and tested home based walking exercise as intervention. The study population was over 55 y of age and received hormone-therapy for breast cancer. After 12 wk the intervention group had lower TST, WT, and movement during sleep; however, no significant change in SE indicative of improved sleep. Similar changes were also seen in subjective sleep scores (PSQI), and serum serotonin was suggested as a possible sleep biomarker.

Study quality and actigraphy methodology

The study quality for the oncological treatment studies ranged from 9 to 16 (scale maximum of 33) with a median of 12 on the risk of bias scale put forth by Downs and Black [25]. Three studies [32,36,38] included controls; one with a properly matched control group [32]; one study used a historic control group [36]; and one study measured out- and inpatients; however, these were not measured during the same time period. Generally the oncological treatment studies were of low quality and of varying design (repeated-measure or cross sectional) (Table 3).

For the sleep intervention studies, the median study quality was 23 with a range 16–23. Of the sleep intervention studies, all the randomized clinical trials [41,42,44,45] had a study quality of 23. The studies included larger study populations, but were negatively affected by data being divided into several publications (e.g., [41,42,44,45,48] presenting data from same study Table 3).

Practical guidelines for the use of actigraphy in a clinical setting have been put forth by the American Academy of Sleep Medicine (AASM) [49]. However, as stated by Berger et al. [24] these guidelines are somewhat limited with regard to procedures in using actigraphy. The review by Berger et al. [24] published in 2008 focused on instrumentation, sampling, data processing, and analysis when using actigraphy. Instrumentation includes information about manufacturer, device model, and placement of the actigraph. Of the 19 studies included, only three studies [32,33,46] did not describe the manufacturer of the actigraph used. Thirteen studies reported using only actigraphs from Ambulatory Monitoring Inc. (Ardsley, New York) and three studies used actigraphs from Philips Respironics Mini Mitter (Bend, OR) (Table 3). Three studies [28,32,46] did not state the device model used (Table 3). Regarding the placement of the actigraph, six studies [27,29–31,33,39] did not report the placement, but in the remaining studies the actigraph was placed on the non-dominant arm. Details about sampling involve describing the patient environment, period of measurement, and the chosen epoch length. All of the nineteen studies reported the environment in which the study was performed, which predominantly was in outpatients in their home environment. A minimum of 3 d of measurement for actigraphy has been recommended [50], and three of the included studies [15,28,33] only measured for 2 d or less. The remaining studies measured for at least 3 d (Table 3). Regarding epoch length 11 studies used 1 min epochs, one study used 30 s epochs, and one study used 15 s epochs, but six studies did not report the epoch length (Table 3). Data processing is an important part of getting correct sleep data, and only nine studies [27–30,34,42,44,45,48] described some kind of data processing albeit heterogeneous in each study. Only two studies [28,38] mentioned which collection mode was chosen and all used zero crossing mode (ZCM). Likewise, few studies [28,51] described which algorithm was used for the sleep analysis, and in these cases it was the Cole–Kripke algorithm. On the contrary only one study [32] did not describe the use of sleep diary to aid in the scoring of actigraphy data.

Discussion

This review provides an overview of studies of patients with cancer receiving oncological treatment where actigraphy has been used to describe sleep outcomes. A total of 19 articles were included in the final review (Fig. 1), out of which 13 had a descriptive study design describing the effect of oncological treatment on sleep, and six included an intervention to improve patients' sleep. Overall, the studies were primarily performed in patients with breast cancer undergoing chemotherapy. In the sleep intervention studies, only breast cancer patients were represented except in one study using a mixed cancer population.

No uniform results were shown in the oncological treatment studies primarily due to heterogeneity in the measuring periods and methodological differences in the actigraphy outcomes reported. Generally TST decreased initially after chemotherapy administration and returned to pre-treatment values before the next administration. No cumulative effect on TST with repeated chemotherapy cycles could be shown. A cumulative effect could however be proved when daytime napping was increased in recovery weeks of cycle 4 in patients with breast cancer. NOA, SE and WASO were also altered, and this change also lasted longer during cycle 4 of treatment. No change in sleep was detected during radiation therapy in the breast cancer population. The gynecological

Table 3
Table of study quality and actigraphy methodology according to Downs and Black [25] and Berger A et al. [24].

Author	Study quality [25]	Manufacture	Device model	Placement	Environment	Duration of recordings	Epoch length	Data processing	Colection mode	Algorithm	Reported outcome	Sleep diary
Liu L et al., 2013 [27]	13	AMI/Philips resp	Actillume/ Actiwatch L	NS	Outpatient	2 × 3 d	1 min	Yes	NS	NS	TST, TWT, NAPTIME	Yes
Dhruva A et al., 2012 [28]	10	AMI	NS	Non-dominant arm	Outpatient	16 × 2 d	30 s	Yes	ZCM	Cole-Kripke	WASO, TST, SL, NOA	Yes
Liu L et al., 2012 [29]	15	AMI	Actillume	NS	Outpatient	5 × 3 d	1 min	Yes	NS	NS	TST, TWT, NAPTIME	Yes
Liu L et al., 2012 [30]	14	AMI	Actilume	NS	Outpatient	7 × 3 d	1 min	Yes	NS	NS	TST, TWT, NAPTIME	Yes
Jim H.S. et al., 2011 [35]	16	Philips resp	Actiwatch	Non-dominant arm	Outpatient	3 × 12 d	NS	NS	NS	NS	TIB, WASO, SE, DS	Yes
Hanisch LJ. et al., 2011 [37]	9	Philips resp	Actiwatch-64	Non-dominant arm	Outpatient	1 × 7 d	15 s	NS	NS	NS	SL,TST, WASO, SE, NAPTIME	Yes
Rissling MB. et al., 2011 [31]	15	AMI	Actilume II	NS	Outpatient	2 × 3 d	NS	NS	NS	NS	TST, SE, NOA and WASO	Yes
Berger AM. et al., 2010 [36]	12	AMI	Octagonal motionlogger	Non-dominant arm	Outpatient	3 × 7 d	1 min	Yes	NS	NS	NOA; WASO-M,WASO-P, SE, and TST.	Yes
Beck sl. Et al. 2010 [34]	12	AMI	Octagonal motionlogger	Non-dominant arm	Outpatient	1 × 3 d	1 min	Yes	NS	NS	TST, NOA, SE and WASO	Yes
Du-Quiton J. et al., 2010 [38]	15	AMI	Mini motionlogger	Non-dominant arm	Hospital/ Outpatient	1 × 4–7 d	1× min	NS	ZCM	NS	WM, SM, TST, SE, WASO, SE, SL	Yes
Payne JK et al., 2006 [32]	11	NS	NS	Non-dominant arm	Hospital/ Outpatient	4 × 3 d	NS	NS	NS	NS	TST	NS
Kuo HH. et al., 2006 [33]	10	NS	Actiwatch	NS	Outpatient	2 × 2 d	NS	NS	NS	NS	TST, SL, WASO and SE	Yes
Miaskowski C et al., 1999 [39]	10	AMI	Mini motionlogger	NS	Outpatient	1 × 2 d	1 min	NS	NS	NS	SL, TIB, TST, NOA and SE.	Yes
Barsevick A et al., 2010 [41]	23	AMI	Octagonal motionlogger	Non-dominant arm	Outpatient	3 d × 2	1 min	NS	NS	NS	TST, SE, NOA, and WASO.	Yes
Berger A. et al., 2009 [42]	23	AMI	Octagonal motionlogger	Non-dominant arm	Outpatient	1 × 2 d + 4 × 7 d	1 min	Yes	NS	NS	TST, SE, NOA, and WASO.	Yes
Berger A. et al., 2009 [45]	23	AMI	Octagonal motionlogger	Non-dominant arm	Outpatient	1 × 2 d + 2 × 7 d	1 min	Yes	NS	NS	TST, SE, NOA, and WASO.	Yes
Berger A. et al., 2009 [44]	23	AMI	Octagonal motionlogger	Non-dominant arm	Outpatient	1 × 2 d + 5 × 7 d	1 min	Yes	NS	NS	TST, SE, NOA, and WASO-P	Yes
Payne JK. Et al. 2008 [46]	16	NS	NS	Non-dominant arm	Outpatient	3 d × 2	NS	NS	NS	NS	SE	Yes
Berger A. et al., 2002 [43]	17	AMI	Mini motionlogger	Non-dominant arm	Outpatient	9 d × 1	NS	NS	NS	NS	TST, SE, NOA, WASO, SL, and NAPS.	Yes

AMI: ambulatory monitoring inc., d: days, DS: daytime sleep, NAPS: naps, NAPTIME: nap time during the day, NOA: number of awakenings, NS: not stated, resp: Respironics, SE: sleep efficiency, SL: sleep latency, SM: sleep minutes, TIB: time in bed, TST: total sleep time, TWT: total wake time, WASO: wake after sleep onset, WM: wake minutes, ZCM: zero crossing mode.

population was the only other population with a genuine longitudinal study design where WASO and daytime sleep where shown to be significantly increased after chemotherapy infusions.

In the sleep intervention studies, cognitive behavioral therapy (ISPP and EASE) and exercise were tested to improve sleep outcomes. Cognitive behavioral therapy (CBT) only showed a significant group × time interaction for NOA (NOA was increased in the intervention group throughout chenotherapy, 30 days, and 60 days post treatment). When patients with breast cancer were grouped according to menopausal status, TST and SE were increased and NOA and WASO reduced in the post menopausal group until 30 d post chemotherapy. CBT is in the general population considered a valid treatment of choice for managing sleep disruption [52], and an initial pilot study in 2010 showed promising results in breast cancer survivors [53]. Fiorentino et al. [53] reported promising results in subjective sleep outcomes, but showed no statistical difference between the groups for objective sleep outcomes (actigraphy). As commented by the authors, the study was limited by a small sample size of 14 and also suffered from considerable dropout in the intervention group. The improvement of sleep outcomes as a result of CBT has not been shown in objective sleep outcomes measured by actigraphy in the current literature.

The investigation of sleep disturbances in patients with cancer has increased during the last decade [1,54]. Recently a national Canadian practice guideline was released focusing on the prevention, screening, assessment, and treatment of sleep disturbances in adults with cancer [21]. The evidence of the guideline is based on 12 randomized controlled trials and three practice guidelines along with expert statements and consensus. The guideline puts forth care path algorithms and recommendations for treatment. An increase in the use of actigraphy in research has been shown in the last few decades [22]. Actigraphy has shown sleep disturbances are present already at the point of surgery [55,56] for the primary cancer, and vary throughout the cancer trajectory [20,55]. Our findings support the presence of sleep disturbances in patients with cancer, and our findings furthermore describe an aggravation of sleep problems during chemotherapy intervention.

When looking at the prevalence of sleep problems, Davidson et al. [2] found a prevalence of insomnia of 31% in a mixed cancer population. However, prevalence of sleep problems in this patient population has been reported with substantial variance ranging between 30 and 87% in the literature [2,7], making it difficult to draw definite conclusions. This variance may be affected by factors such as the diagnoses of cancer, severity of the cancer, side-effects of oncological treatment, and psychological and/or physical comorbidity of the individual patient [57]. Our results also suffer from conflicting outcomes of which TST is a good example. TST was at the same time point in the breast cancer population reported to be increased [27], unchanged [29], and decreased [31] compared to baseline values. Even though the measurement was performed within a similar population receiving comparable oncological treatment, the populations may still vary on demographic values such as age or menopausal status. The effect of age on sleep in patients with cancer has repeatedly [2,20] shown an opposite relationship compared to the general population. In cancer populations, young age is associated with increased reporting of insomnia, and this could be explained by younger patients having more aggressive tumors and/or receive more aggressive treatment [20]. Menopausal status and the effect of hot flashes have been reported to affect sleep in a negative manner [58]. In a recent study of patients with breast cancer [59] it was shown that nocturnal hot flashes and sleep disturbances (determined by PSG) co-occurred, and it was suggested that they may share a common central regulation from the central nervous system. As pointed out by Palesh et al. [7], future research should strive to differentiate between the influence of tumor (e.g., the specific cancer) and the cancer treatment. To be able to eliminate these confounding factors, dedicated studies performed on large homogenous populations (i.e., unique cancer, similar age, stratified for menopausal status) in a standardized treatment setup regarding measuring pretreatment baseline sleep outcomes, are needed.

The papers included in the review were not of the highest quality. The oncological treatment studies generally had low quality, and often lacked healthy matched controls. The sleep intervention studies had moderate quality, but were nearly uniformly performed in patients with breast cancer. Therefore, more studies are needed on other cancer populations such as lung, gastrointestinal, head and neck, gynecological, and urological patients. With regard to the methodology of actigraphy, a large number of studies included information about actigraph details and sampling. However, the procedures for data processing and analysis were only sparsely reported, which is of major importance for outcome measures and generalizability of the findings. Future studies should strive to use standardized procedures and, at the least, describe them in detail to make results more transparent and comparable across studies.

Objective sleep can be determined by both PSG and actigraphy with each methodology having its advantages. Actigraphy is non-invasive and ideal for measuring in an outpatient setting (i.e., the habitual setting) [23], whereas with PSG one can describe the sleep architecture and not just the absolute sleep values. In a recent review it was shown that only 23% of intervention studies in patients with cancer use both subjective and objective sleep measures [1]. One would expect subjective and objective sleep measures to be coherent and show similar results as they set out to measure the same outcome. However, two of the oncological treatment studies [28,34] included in this review reported moderate to low correlations between subjective and objective parameters. Furthermore, when looking at the sleep intervention studies using CBT [41,42,44,45,48], the improvements in sleep were predominantly present in the subjective sleep measures. This lack of effect on objective sleep outcomes in these studies is explained by a flooring-effect i.e., the objective outcomes already were close to normal so the room for improvement was limited. As the studies did not measure healthy appropriatly matched controls, one cannot know if this was the case. The same discrepancy was also shown between PSG and subjective sleep measures in breast cancer survivors [60]. Overall, it seems like subjective and objective sleep measures do not describe exactly the same dimension of sleep, but more likely different aspects of the diverse outcomes that make up sleep disturbances. Along with older recommendations [1], future research should imply both subjective and objective sleep measures to give a more complete picture of sleep disturbances. The subjective measures used in cancer populations should be validated with clinically relevant cut-off values (i.e., PSQI or insomnia severity index – ISI) [7], and objective sleep measures should fit the purpose of the study (i.e., actigraphy for ambulatory monitoring and PSG for description of sleep architecture).

In conclusion, sleep disturbances are a prevalent and persistent issue for patients with cancer as determined objectively by actigraphy. The sleep disturbances seem to be aggravated by chemotherapy treatment and accumulate as the treatment continues. In light of this, sleep disturbances are something clinicians working with patients with cancer need to pay extra attention to, and if possible screen their patients throughout the cancer trajectory [21]. A limited number of studies have tested non-pharmacological interventions (CBT) effect on sleep whose effect was most evident in subjective sleep outcomes compared to objective sleep measures.

More research is needed in other cancer populations than patients with breast cancer as they have not gained sufficient

attention. Actigraphy is a relevant methodology that can be used in cancer patients, making measurement for extended time periods in a home setting possible. Further work should strive to abide by the guidelines from the AASM [49] and by Berger et al. [24] which would make results more valid and make cross study comparison easier. Furthermore future studies should use both objective and subjective outcome measures to describe the complexity of sleep disturbances.

Practice points

1. Sleep disturbances are very common in patients undergoing oncological treatment. Actigraphy can serve as a tool to help identify patients with sleep disturbances and to monitor effects of oncological treatment.
2. As the chemotherapy regime continues through several series, the sleep disturbances seem to aggravate. Therefore, screening and sleep assessment is warranted throughout the entire chemotherapy regime.
3. Non-pharmacological interventions designed to alleviate sleep disturbances in the patient population primarily showed an effect on subjective outcomes, and not objective outcomes.

Research agenda

1. More research is warranted in other cancer populations beside patients with breast cancer.
2. Future work should strive to include ambulatory polysomnography to further describe the sleep disturbances in an oncological population to increase the understanding of cancer related insomnia.
3. Future work should also test pharmacological interventions to reduce sleep disturbances in a randomized clinical setup (interventions like chronobiotics or hypnotics).
4. Longitudinal studies are needed to clarify if sleep disturbances in patients with cancer is a prognostic factor for the further cancer trajectory.

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